

REMARKS

Reconsideration and withdrawal of the objections to and the rejections of this application in view of the amendments and remarks herewith, is respectfully requested, as the changes place the application in condition for allowance.

I. Status of the Claims and Formal Matters

Claims 1-20, and 23-26 are under examination in this application. Claims 1, 12 and 17 have been amended, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. Original claim 8 has now been cancelled. No new matter has been added by these amendments. Support for these amendments is found throughout the specification and in the original claims (in particular, original claim 8). New claim 26 has been added. Support for new claim 26 can be found on page 4 of the specification.

Executed forms for a Revocation of Power of Attorney with New Power of Attorney and a Change of Correspondence Address will be filed as soon as possible.

II. THE REJECTIONS UNDER 35 U.S.C. § 102(B) ARE OVERCOME

The Office Action rejected claims 1-14, 17-20 and 23 as allegedly being anticipated by Khadem (U.S. Patent No. 5,552,452). The Applicants maintain their position that the limited description provided in the specification of Khadem is not enabling for methods of creating a tissue seal without the use of an exogenous cross-linkable substrate. Accordingly, this rejection is respectfully traversed.

A. Declaration of Michael Hamblin

The Declaration of Michael R. Hamblin Ph.D. Under 37 C.F.R. § 1.132 ("the Hamblin Declaration"), submitted on April 12, 2004, provided evidence of non-enablement of the Khadem disclosure as it pertains to a method of adhering tissue without an exogenous peptide or protein. The Hamblin Declaration was considered by the Examiner, but deemed to be "rebuttal evidence of nonobviousness" and not anticipation. See page 3 of the July 19, 2004 Office Action ("the Office Action"). Office Action states at page 2 "the Applicant is using an argument of non-obviousness in trying to overcome an anticipatory rejection." The record indicates that the Hamblin Declaration was not considered for its bearing on enablement.

It is believed that clarifying the proper legal standard to be applied in assessing whether or not a cited prior art reference provides an enabling disclosure would be helpful in furthering prosecution of the instant application. To begin, the relevant section of the Manual of Patent Examining Procedure is provided below:

2121.01 Use of Prior Art in Rejections Where Operability Is in Question

A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985).

According to M.P.E.P. § 2121.01, proof of non-enablement depends on whether "one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention." If not, the reference is inoperable and therefore, not enabled. After a determination of non-enablement is made by an examiner, the

reference in question is removed from consideration as prior art under 35 U.S.C. § 102. See *Chester v. Miller*, 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003) ("A claimed reference cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled."). *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968) ("In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'...").

The Federal Circuit has also pronounced that a reference does not contain an enabling disclosure if a person of ordinary skill in the art could not have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003); *In re Sun*, 31 U.S.P.Q.2D 1451, 1452 (Fed. Cir. 1993), *In re Donohue*, 766 F.2d 531 (Fed. Cir. 1985); *In re Sasse* 629 F.2d 675, 681 (C.C.P.A. 1980), *In re Borst*, 345 F.2d 851, 855 (C.C.P.A. 1962). Therefore, it is respectfully requested that the Hamblin Declaration be reconsidered as rebuttal evidence under 35 U.S.C. § 102, with application of the standard adopted by the Office in M.P.E.P. § 2121.01.

A reference is presumed operable until an Applicant provides facts rebutting the presumption of operability. *In re Sasse*, 629 F.2d 675, (C.C.P.A. 1980). An expert declaration providing facts sufficient to establish that the cited reference cannot be used to practice the claimed invention will overcome the presumption of operability. See *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). In Professor Hamblin's expert opinion, Khadem does not provide one of ordinary skill in the art with the necessary disclosure to combine the Khadem description with his own knowledge to practice the claimed invention. Thus, according to the evidence of record, Khadem fails the test for enablement.

B. Further Evidence In Support of the Hamblin Declaration

With regard to the claimed invention, Khadem teaches only as follows:

"The present invention also encompasses methods for tissue closing or wound healing wherein the actual preparation of a separate protein or peptide containing composition is not

necessary. Such methods utilize the peptides or proteins located naturally within the tissue area as in situ protein containing compositions. To form an adhesive connection between biological tissues in this manner one would form a biologically effective amount of a tissue adhesive combination at the tissues **by applying only the photosensitizer component to the tissues**. One would then again apply electromagnetic radiation the tissue adhesive combination thus formed in a manner effective to promote the formation of an adhesive connection between the tissues." Column 7 lines 18-30 (emphasis added).

Table 2 also indicates that experimentation was conducted with Rose Bengal, either with or without albumin. The methods and results are not described.

The above-referenced sentences in Khadem, even when read together with the remaining portions of the specification, fail to enable the claimed invention for at least three reasons:

1. Khadem provides no teaching of specific tissues in which bonding will be effective in the absence of an exogenous cross-linkable substrate;
2. Khadem provides no exemplification of a means for creating a tissue seal in any tissue without an exogenous cross-linkable substrate; and
3. Khadem provides no teaching of specific photosensitizers (or excitation wavelengths or fluences thereof) that will be effective in tissue bonding without an exogenous cross-linkable substrate and without thermal damage.

Thus, a person of ordinary skill in the art could not have combined Khadem with his own knowledge of the art to have acquired possession of the claimed invention.

In further support of the Hamblin Declaration and the arguments presented herein, it is submitted that the teaching in Table 1 of Khadem is flawed as to the use of Rose Bengal. In Table 1, Khadem teaches excitation of Rose Bengal at 600-670 nm. However, Rose Bengal is not active within this wavelength range as it does not absorb light within this spectrum. (See Figure 1, Lambert et al., (1999) J. Phys. Chem. B, Vol. 103 No. 18, enclosed under Tab 1). The first law of photochemistry provides that light must be absorbed for a photochemical reaction to occur. Accordingly, not only does Khadem fail to enable combined non-substrate/non-thermal based tissue bonding, in this instance, it fails to enable any bonding whatsoever.

The prosecution history of the Khadem patent is even more telling. A declaration submitted on August 3, 1995 by John Khadem, M.D., a co-inventor of the Khadem patent, describes his own perceived requirements for operability (referred to herein as the "Khadem Declaration," a copy of which is enclosed under tab 2). In the Khadem Declaration, an exogenous protein substrate concentration of at least 1% is described as a critical ingredient of photoactivatable compositions for use in tissue bonding. Khadem states "compositions below 1% protein (1% = 10 mg/ml) are not sufficiently viscous to produce adhesive properties upon photoactivation."

Thus, as stated by Dr. Hamblin and as supported by the documentary evidence provided herein, the description in Column 7 lines 18-30 and Table 2 of Khadem lack enablement for the claimed methods and the remaining disclosure in Khadem does not fill the gap.

C. Other Evidence of Inoperability

Evidence which shows unsuccessful attempts by others to achieve the inventor's results before the date of the invention will be adequate to show inoperability of an alleged prior art reference. *In re Wiggins*, 488 F.2d 538 (C.C.P.A. 1971). In *Wiggins*, attempts to make claimed compounds using the prior art methods were all unsuccessful. As noted by M.P.E.P. § 2121.02, the Court considered this evidence sufficient proof of non-enablement of a cited prior art reference.

The Examiner's attention is directed to (Bass & Treat (1995) *Lasers Surg Med* 17: 315-49), which was made of record in the Information Disclosure Statement submitted on June 19, 2002. Bass & Treat provide a discussion of attempts by others to achieve the inventor's results without use of exogenous cross-linkable substrates. See page 330 of Bass & Treat. Upon comparison, it can be seen that these attempts were unsuccessful due to the use of thermal welding techniques.

While several investigators in the field, including Khadem, favored the use of substrates in tissue bonding (substrates were often referred to as "tissue glue" for their adhesive effect), others attempted to avoid this practice due to the scarring that would develop.¹ As one example,

¹ Methods for adhering tissues with an exogenous cross-linkable substrate are disadvantageous for several reasons. First, the exogenous cross-linkable substrate is a filler material that creates gaps when added to the tissue and

practitioners described by Bass & Treat conducted the initial steps of tissue bonding as claimed herein—without use of exogenous cross-linkable substrates. However, thermal welding was subsequently applied to the tissue photosensitizer complexes because it was commonly believed to be required for adequate bonding where no substrate was used. Consequently, the undesirable side effects of thermal welding developed. See page 330 of Bass & Treat; Bass et al., (1992) *Lasers Surg Med* 12: 500-505. Thus, others who have tried to conduct tissue bonding without use of exogenous cross-linkable substrates have failed to achieve the results of the claimed invention.

Khadem does not provide guidance for methods of photochemical tissue bonding as claimed herein (i.e., without thermal bonding and substrate use) and therefore, is not enabled for the claimed methods. Thus, the failure of Bass & Treat further illustrates the non-enablement of Khadem.

D. Effect of Claim Limitations

To form the basis of a proper rejection under 35 U.S.C. § 102(b), a cited reference must disclose each and every element of the rejected claim(s). See *Lewmar Marine Inc. v. Barient Inc.*, 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Khadem fails to disclose each and every element of the claimed invention and therefore, should be removed from consideration as a reference under 35 U.S.C. § 102(b).

The Examiner's attention is directed to amended claim 1, which contains the following recitation (claims 12 and 17 contain a similar recitation):

“applying electromagnetic energy at a wavelength of at least about 488 nm to the tissue-photosensitizer mixture in a manner effective to produce cross linking of a protein in the tissue without producing substantial thermal damage, wherein the tissue is not contacted with an exogenous cross-linkable substrate”

subsequently cross-linked. These gaps can fill with fibrotic material, therefore resulting in inflammation and scar formation. Second, the exogenous material that is not native to the tissue forms an amorphous bridge between tissues that must be remodeled by the body. Such tissue remodeling can also result in inflammation and scar formation. Third, any time an exogenous material is added to a tissue, the regular structure of the tissue is lost, which can also result in inflammation and scar formation.

Nowhere in Khadem is it disclosed that electromagnetic energy having a wavelength of at least 488 nm can be applied to a tissue-photosensitizer complex in a manner that avoids thermal bonding and yet still produces bonded tissue without an exogenous cross-linkable substrate. Column 7 lines 18-30 and Table 2 of Khadem lack an indication of the proper pairing between a photosensitizer and an excitation wavelength and moreover, Table 1 discloses an inoperable pairing. There is no description in Khadem of the power or fluences to be used in conducting non-thermal tissue bonding without an exogenous cross-linkable substrate (as noted on page 5 of the Office Action). Therefore, Khadem, as a single reference, fails to supply each and every element of the claimed invention.

As noted in the Office Action, on page 3, the claimed methods must distinguish from the inoperative reference disclosure (i.e., Khadem). It is respectfully submitted that the above-referenced recitation distinguishes from the inoperative disclosure in Khadem.

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 102 is respectfully requested.

II. THE REJECTIONS UNDER 35 U.S.C. § 103(A) ARE OVERCOME

A. Rejection of Claims 15-17 and 32-34.

Claims 15-16 and 24-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Khadem. Claims 15-16 and 24-25 relate to ranges of time, energy doses and irradiances to be used in delivering light. These ranges are alleged to be the result of routine optimization by the skilled artisan and therefore obvious given the teaching by Khadem. See page 4 of the Office Action. Applicants respectfully traverse the rejection.

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986); *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-08 (Fed. Cir. 1991). Thus, evidence showing that there was no reasonable expectation of success can support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048 (C.C.P.A. 1976).

Claims 15-16 and 24-25 encompass methods of photochemical tissue bonding that exclude the use of an exogenous cross-linkable substrate as well as the use of thermal bonding. As the teachings of Bass & Treat and the Khadem Declaration show, such methods were viewed as suspect by those skilled in the art. Not only do these documents provide evidence that there was no reasonable expectation of success in practicing the claimed methods but also, show that the applicants proceeded contrary to accepted wisdom in the art. Pursuing an inventive course that is contrary to accepted wisdom in the art is also persuasive evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038 (Fed. Cir. 1986).

A reasonable expectation of success may exist where the prior art is particularly instructive. See *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). In *O'Farrell*, the Court of Appeals for the Federal Circuit determined that the claimed method would have been obvious over the prior art relied upon because the prior art contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and suggested that the modification would be successful.

In contrast to the cited prior art in *O'Farrell*, Khadem contains none of these traits. Nowhere in Khadem is there teaching or suggestion that electromagnetic energy having a wavelength of at least 488 nm can be applied to a tissue-photosensitizer complex in a manner that avoids producing substantial thermal damage and yet still produces bonded tissue without an

exogenous cross-linkable substrate. There is no description in Khadem of the time, power or fluences to be used in conducting non-thermal tissue bonding without an exogenous cross-linkable substrate. Consequently, Khadem provides no reasonable expectation of success in practicing the claimed methods. *See also* the Hamblin Declaration at page 2, paragraphs 4 and 5; page 3, paragraphs 5 and 6.

If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Claims 15-16 and 25 depend from claim 12 and claim 24 depends from claim 1. As the disclosure in Khadem and the knowledge in the art provides no reasonable expectation of success in practicing claims 1 and 12, thereby establishing the nonobviousness of claims 1 and 12, claims 15-16 and 24-25 are by extension also nonobviousness.

Reconsideration and withdrawal of the rejections of claims 15-16 and 24-25 under 35 U.S.C. § 103 is respectfully requested.

REQUEST FOR INTERVIEW

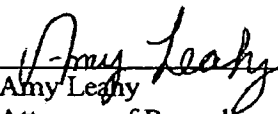
If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested; and, the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the amendments and remarks herewith, the application is in condition for allowance. Favorable reconsideration of the application, reconsideration, and withdrawal of the objections to and rejections of the application, and prompt issuance of a Notice of Allowance are respectfully requested.

Respectfully submitted,

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